REMARKS

Claims 1, 19 and 20 have been amended, claims 10-16, 27-28, and 31-34 have been cancelled, and claims 4, 6, 21, 23, and 30 are withdrawn herein. Thus, claims 1-9, 17-26, and 29-30 are currently pending. The amendments to the claims and specification are fully supported by the original claims and specification and were made to simply correct typographical errors and include the generic names as requested by the Examiner. No new matter has been added. Entry of the amendments at this time is therefore respectfully requested. Applicant reserves the right to pursue any of the cancelled claims in one or more continuation applications.

The Examiner rejected claims 13 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 13 and 14 have been cancelled. In view of this, the rejection is now moot and should be withdrawn.

Claims 1-11, 17-19, 21, 23 and 25-30 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11, 13, 14, 16-24 and 29-32 of copending Application No. 11/494,362 for the reasons set forth on pages 3-4 of the Office Action. Applicant will file a terminal disclaimer upon allowance of the claims, if one is necessary at that time. Furthermore, Applicant is willing to maintain a clear line of demarcation between the applications going forward.

Claims 1, 2, 4, 5, 7-11, 14, 17-24 and 26-30 were also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-18, 20, 21, and 24-36 of copending Application No. 11/104,422 for the reasons set forth on pages 4-5 of the Office Action. Applicant will file a terminal disclaimer upon allowance of the claims, if one is necessary at that time. Furthermore, Applicant is willing to maintain a clear line of demarcation between the applications going forward.

Claims 1, 2, 5, 7-11, 13, 14, 19-21 and 24-28 were rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenbrand et al. WO 00/61555 in view of Alternative Medicine Review (2002) and in further view of Drug Facts and Comparisons (1994) for the reasons set forth on pages 6-8 of the Office Action.

Applicant has amended the claims in an effort to expedite the eventual allowance of the claims. The amended claim is specifically directed to a method of treating Crohn's disease or ulcerative colitis by administering at least one compound of formula I, II, or III to an animal in need of such treatment. Claim 1 further requires that the compound be administered in an

amount sufficient to treat the inflammatory-related disease by inhibiting pro-inflammatory cytokine expression or by stimulating anti-inflammatory cytokine expression, but the amount must be less than sufficient to substantially inhibit cyclin dependent kinases.

Eisenbrand et al. is directed to active substances which are used in the treatment of solid tumors and metastases. Eisenbrand does not teach and is not directed to the treatment of method of treating, an inflammatory bowel disease, e.g., Crohn's disease or ulcerative colitis. This is very different than the treatment of cancer, solid tumors, as taught by Eisenbrand. One skilled in the art would not reasonably expect the compounds of the invention to be effective at treating inflammatory bowel disease based on Eisenbrand. Eisenbrand does not teach or even suggest a treatment for Crohn's disease or ulcerative colitis. In addition, Eisenbrand also fails to teach or suggest the administration of a compound of formula I, II, or III in an amount sufficient to treat the inflammatory-related disease by inhibiting pro-inflammatory cytokine expression or by stimulating anti-inflammatory cytokine expression, but the amount must be less than sufficient to substantially inhibit cyclin dependent kinases as specifically required by claim 1. Without such teachings it cannot make the presently claimed invention unpatentable.

Furthermore, the Alternative Medicine Review article cited by the Examiner does not remedy the deficiencies of Eisenbrand et al. First, the Alternative Medicine Review article is directed to Isatis tinctoria and its use as a COX-2 inhibitor in general, not the presently pending invention, a method of treating Crohn's disease or ulcerative colitis. The article also does not identify any of the compounds as presently claimed for treatment of a method of treating Crohn's disease or ulcerative colitis. The article also fails to mention the limitation of claim 1 requiring that the amount to be administered must be less than sufficient to substantially inhibit cyclin dependent kinases, as presently claimed.

Finally, the article attributes the Isatis COX-2 inhibitory properties to the fact that Isatis leaves have an alkaloid known as tryptanthrin, which is strongly inhibitory to the COX-2 enzyme, stating that it "is theorized to be largely responsible for the anti-inflammatory action of Isatis." While indirubin, a compound found in Isatis root, is attributed to have anti-cancer activity by inhibiting DNA replication in neoplastic cells without causing significant marrow suppression.

Thus, the article cannot be said to make the present invention unpatentable as being obvious in combination with Eisenbrand et al. As neither reference mentions that treatment of an

inflammatory bowel disease, e.g., Crohn's disease or ulcerative colitis, they cannot make the presently claimed invention unpatentable alone or in combination. Applicant was the first to discover and teach and demonstrate a successful method of treating Crohn's disease or ulcerative colitis as presently claimed. As Applicant was the first to discover and teach the presently claimed method of treating inflammatory bowel disease, they are entitled to obtain patent protection for the same.

The Examiner also rejected claims 1-11, 13, 14, and 17-30 under 35 U.S.C. § 103(a) as being unpatentable over Kunikata et al. (C3 from IDS dated 8.15.05), Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenyujo EP 0 987 027 A1 (B1 from IDS dated 8.15.05) and Drug Facts and Comparisons (1994) and in further view of Liu (C47 from IDS dated 1.16.08) for the reasons stated on pages 6-12 of the Office Action.

Kunikata investigated indirubin isolates from *Polygonum tinctorium* plants and the effects of indirubin (only) on 2,4, 6-trinitro-1-chlorobenzene (TNCB) induced delayed-type hypersensitivity (DTH), e.g., an allergic reaction. Treatment of DTH is very different than the treatment of a chronic disease, such as, inflammatory bowel disease. DTH reactions are antigen-specific, cell-mediated immune responses which depend on the specific antigen involved. A DTH response is an inflammatory response that develops 24 to 72 hours after exposure to an antigen that the immune system recognizes as foreign. DTH reactions involve mainly T cells, rather than antibodies generated from B cells. See, for example, (http://www.cancer.gov/templates/db_alpha.aspx?CdrID=44587).

In contrast, the presently claimed invention is directed to a method of treating an inflammatory bowel disease, e.g., Crohn's disease or ulcerative colitis, a chronic disease. Treatment of a chronic disease is very different than an *in vitro* study relating to a delayed-type hypersensitivity reaction. Treatment of Crohn's disease or ulcerative olitis is much more complex and involves the ongoing treatment of an out-of balance immune system over an extended duration *in vivo*. Kunikata is limited to the effects of indirubin specifically (which is not covered by the claims) and specifically it effects relating to DTH. Kunikata actually teaches away from the successful treatment of chronic diseases, teaching that the effects of indirubin gradually diminished upon repeated elicitation (Fig. 6, page 97). This clearly teaches that indirubin, which the claims do not cover, would not be useful for the treatment of a chronic disease, requiring ongoing and continued treatment, contrary to DTH as taught by Kunikata.

Even in the single elicitation experiments of DTH, indirubin was significantly less effective than the positive control (Results 3.3., Figs.5 and 6), and further diminished as it was repeated.

Furthermore, to treat a chronic out-of-balance immune system such as inflammatory bowel disease, the treatment must involve not only inhibition of pro-inflammatory cytokines, but also the stimulation of anti-inflammatory cytokines. Kunikata clearly does not teach this. See Results 3.1 and 3.3, wherein indirubin had no affect on IL-4 production *in vitro* (Fig. 3B) as well as *in vivo* (Results 3.3, Fig. 7B). Just because a compound inhibits IL-6, it does not necessarily mean it would inhibit other pro-inflammatory cytokines and definitely does not indicate that it would stimulate expression of anti-inflammatory cytokines necessary to treat chronic bowel disease as presently claimed.

In addition, Kunikata reported that the indirubin inhibited the production of interferon-γ and interleukin-6 by murine splenocytes *in vitro*, but not *in vivo*. These *in vitro* results are extremely limited. All those skilled in the art understand that just because a compound is effective *in vitro* for a particular purpose, definitely does not indicate it will be effect for the same purpose *in vivo*. Applicant was the first to discover the presently claimed method of treating a chronic disease, such as inflammatory bowel disease.

In view of the above, Kunikata clearly would not lead one skilled in the art to a responsible expectation of success of treating an animal suffering from Crohn's disease or ulcerative colitis as presently claimed with the compounds as claimed. Although interferon-γ and interleukin-6 are involved at times in inflammation in some ways, numerous studies have demonstrated that targeting interferon-γ and interleukin-6 alone is not effective in treating long term bowel diseases that involve sophisticated cytokine network and continued treatment. This is evident in the findings of Kunikata mentioned above (Fig. 6, page 97).

Applicant was the first to show that administering the compound of formula IV, V, or VI was able to rebalance the cytokine network thereby treating the complex aspects of inflammatory bowl disease *in vivo*. For these reasons, Kunikata fails to make obvious the presently claimed method of treating inflammatory bowel disease, e.g., Crohn's disease or ulcerative colitis as presently claimed. Again, Applicant was the first to discover and enable the presently pending method of treating Crohn's disease and ulcerative colitis.

Kabushiki (EP 0 987 027) fails to remedy the deficiencies of Kunikata. Kabushiki is directed to physiologically active extracts from *Polygonum tinctorium*. The extract includes

ethyl acetate-soluble ingredients including tryptanthrin, 3,5,4'-trihydroxy-6,7-methylenedioxy-flavone, kaempferol, 3,5,7,4'-tet-rahydroxy-6-methoxy-flavone, gallic acid, caffeic acid, indirubin, pheophorbide a, methylpheophorbide a, and other compounds Kabushiki did not specifically identify. It is difficult to attribute any of specific pharmaceutical attributes to any particular compound in the plant extract as there are so many compounds in the extract and the combinatory effect of multiple compounds that is typical. At paragraph 23, it appears that the plant extract is good for treating almost all human aliments (bacterial diseases, viral disease, cancer, shock, fungal disease, Alzheimer's disease AIDS, habitual alcohols, respiratory disorders, etc.). From this it is evident that Kabushiki was not enabled for the successful treatment of all of these diseases with this plant extract, which had numerous combinations of compounds therein. Kabushiki clearly does not remedy the deficiencies of Kunikata, and thus, does not make obvious the presently pending claims directed specifically to the treatment of a patient suffering from chronic inflammatory bowel disease. Thus, from this, one skilled in the art would not have a reasonable expectation of success of treating Crohn's disease or ulcerative colitis, with the compounds of the present invention, which do not include indirubin.

Liu is directed to the treatment of leukemia using meisoindigo. Just because a drug is more successful at treating one disease, e.g., leukemia, provides no indication whatsoever that the drug would be effective at all at treating an entirely different chronic disease, such as inflammatory bowel disease as presently claimed. This is clearly understood by one skilled in the art. Furthermore, one skilled in the art would be anxious to administer a drug that is effective at treating leukemia to a patient that does not have leukemia, as such drugs may have significant side effects. Based on the teachings of Liu alone, or in combination with Kunikata or any of the above references, one skilled in the art would not have a reasonable expectation of success of successfully treating Crohn's disease or ulcerative colitis as presently claimed and thus, Liu cannot make the presently claimed invention obvious alone or in combination with the above references.

Again Kunikata is directed to the effects of indirubin on 2,4, 6-trinitro-1-chlorobenzene (TNCB) induced delayed-type hypersensitivity (DTH), e.g., an allergic reaction. Treatment of DTH is very different than treatment of chronic diseases, such as, a chronic bowel disease. In fact, as mentioned above, Kunikata actually teaches away from the presently claimed invention involving the treatment of chronic bowel disease, teaching that the effects of indirubin gradually

diminished upon repeated elicitation (Fig. 6, page 97). This clearly teaches that indirubin would not be useful for the treatment of a chronic disease requiring ongoing and continued treatment. Furthermore, to treat a chronic out-of-balance immune system *in vivo*, such as Crohn's disease or ulcerative colitis, the treatment must involve not only inhibition of pro-inflammatory cytokines, but also the stimulation of anti-inflammatory cytokines, which Kunikata does not teach. See Results 3.1 and 3.3, wherein indirubin had no affect on IL-4 production *in vitro* (Fig. 3B) as well as *in vivo* (Results 3.3, Fig. 7B). Liu does nothing to remedy these deficiencies and is specifically directed to treatment of leukemia, a completely unrelated disease.

As the prior art cited above does not teach or suggest the presently claimed invention alone or in combination, Applicant respectfully requests that this rejection be withdrawn.

In view of the above, Applicant believes all claims to be in condition for allowance. If there are any questions, the Examiner is invited to call Applicant's representative Rodney Fuller at (602) 916-5404 to resolve any remaining issues to expedite the allowance of this application.

Respectfully submitted,

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Date

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